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(54) Title: ANTISENSE OLIGONUCLEOTIDE CHEMOTHERAPY FOR BENIGN HYPERPLASIA OR CANCER OF THE PROSTATE

(57) Abstract

Methods of selectively inhibiting the growth of or killing prostatic cells, using antisense oligonucleotides to prostate specific genes, are disclosed. The oligonucleotides may have natural nucleic acid structures or may be modified oligonucleotides with enhanced stability or tissue specific targeting. The prostate specific genes to which the antisense may be directed include the AR and the αFGF gene. Pharmaceutical compositions including such antisense oligonucleotides are also described for use in the methods. The methods and products are of particular utility in the treatment of benign prostatic hyperplasia or prostate cancer.

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| NL | Netherlands |
| NO | Norway |
| NZ | New Zealand |
| PL | Poland |
| PT | Portugal |
| RO | Romania |
| RU | Russian Federation |
| SD | Sudan |
| SE | Sweden |
| SG | Singapore |
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# ANTISENSE OLIGONUCLEOTIDE CHEMOTHERAPY FOR BENIGN HYPERPLASIA OR CANCER OF THE PROSTATE

## Summary of the Invention

The present invention provides methods for treating a patient diagnosed as having benign prostatic hyperplasia or a prostatic cancer. The methods include administering to the patient a therapeutically effective amount of a composition comprising an antisense oligonucleotide which selectively hybridizes to an AR or αFGF gene or mRNA sequence of the patient, thereby inhibiting the expression of the AR or αFGF gene or mRNA sequence. This inhibition of the AR or αFGF genes or mRNAs by antisense oligonucleotides results in a significant inhibition of the growth or survival of prostatic cells. As a result, the methods provide a useful new means of treating benign prostatic hyperplasia and prostatic cancer. The methods are particularly useful in treating prostate cancer patients who have become refractory to anti-androgen hormonal therapy.

The AR antisense oligonucleotides may comprise at least 10 consecutive bases from SEQ

ID NO.: 1, at least 10 consecutive bases from a genomic sequence corresponding to SEQ ID NO.: 1, or oligonucleotides that hybridize to the complements of these sequences under physiological conditions. More preferably, the antisense oligonucleotides comprise at least 15 consecutive bases, and most preferably, 20-30 consecutive bases from the above-described sequences.

As will be understood by one of ordinary skill in the art, the antisense oligonucleotides of the present invention need not be perfectly complementary to the AR or αFGF genes or mRNA transcripts in order to be effective. Rather, some degree of mismatches will be acceptable if the antisense oligonucleotide is of sufficient length.

Of particular importance in this respect is the use of self-stabilized or hairpin oligonucleotides. Such oligonucleotides, or modified oligonucleotides, have a sequence at the 5' and/or 3' end which is capable of folding over and forming a duplex with itself. The duplex region, which is preferably at least 4-6 bases joined by a loop of 3-6 bases, stabilizes the oligonucleotide against degradation. These self-stabilized oligonucleotides are easily designed by adding the inverted complement of a 5' or 3' AR or αFGF sequence to the end of the oligonucleotide (see, e.g., Table 1, SEQ ID NO.: 6 and SEQ ID NO.: 7; Tang, J.-Y., et al. (1993) Nucleic Acids Res. 21:2729-2735).

In another series of embodiments, a recombinant gene is constructed which encodes an

AR or αFGF antisense oligonucleotide and this gene is introduced within the targeted cells on a vector. Such an AR or αFGF antisense gene may, for example, consist of the normal AR or αFGF sequence, or a subset of the normal sequences, operably joined in reverse orientation to a promoter region. An operable antisense gene may be introduced on an integration vector or may be introduced on an expression vector. In order to be most effective, it is preferred that the antisense sequences be operably joined to a strong eukaryotic promoter which is inducible or constitutively expressed.

gene (SEQ ID NO.: 1). SEQ ID NO.: 6 is a self-stabilized or hairpin oligonucleotide. The first 21 bases are complementary to positions 916-936 of the AR gene. The remaining eight are identical to positions 920-927 of the gene, allowing formation of a 3' hairpin. SEQ ID NO.: 7 is another self-stabilized antisense oligonucleotide. The first 21 bases of this oligonucleotide are complementary to positions 927-947 of the AR gene. The remaining eight are identical to

positions 931-938 of the gene, allowing for formation of a 3' hairpin.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: WORCESTER FOUNDATION FOR BIOMEDICAL RESEARCH, INC.

(ii) TITLE OF INVENTION: ANTISENSE OLIGONUCLEOTIDE CHEMOTHERAPY FOR BENIGN HYPERPLASIA OR CANCER OF THE PROSTATE

(iii) NUMBER OF SEQUENCES: 8

(iv) CORRESPONDENCE ADDRESS:

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(B) STREET: 600 ATLANTIC AVENUE

(C) CITY: BOSTON

(D) STATE: MA

(E) COUNTRY: USA

(F) ZIP: 02210

(v) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Floppy disk

(B) COMPUTER: IBM PC compatible

(C) OPERATING SYSTEM: PC-DOS/MS-DOS

(D) SOFTWARE: PatentIn Release #1.0, Version #1.25

(vi) CURRENT APPLICATION DATA:

(A) APPLICATION NUMBER:

(B) FILING DATE:

(C) CLASSIFICATION:

(viii) ATTORNEY/AGENT INFORMATION:

(A) NAME: TWOMEY, MICHAEL J.

(B) REGISTRATION NUMBER: 38,349

(C) REFERENCE/DOCKET NUMBER: W0461/7035

(ix) TELECOMMUNICATION INFORMATION:

(A) TELEPHONE: 617-720-3500

(B) TELEFAX: 617-720-2441

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 3569 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: double

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:

(A) ORGANISM: HOMO SAPIENS

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 363..3122

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

TAATAACTCA GTTCTTATTT GCACCTACTT CAGTGGACAC TGAATTTGGA AGGTGGAGGA 60

TTTTGTTTTT TTCTTTTAAG ATCTGGGCAT CTTTTGAATC TACCCTTCAA GTATTAAGAG 120

ACAGACTGTG AGCCTAGCAG GGCAGATCTT GTCCACCGTG TGTCTTCTTC TGCACGAGAC 180

TTTGAGGCTG TCAGAGCGCT TTTTGCGTGG TTGCTCCCGC AAGTTTCCTT CTCTGGAGCT 240

TCCCGCAGGT GGGCAGCTAG CTGCAGCGAC TACCGCATCA TCACAGCCTG TTGAACTCTT 300

CTGAGCAAGA GAAGGGGAGG CGGGGTAAGG GAAGTAGGTG GAAGATTCAG CCAAGCTCAA 360

GG ATG GAA GTG CAG TTA GGG CTG GGA AGG GTC TAC CCT CGG CCG CCG 407
Met Glu Val Gln Leu Gly Leu Gly Arg Val Tyr Pro Arg Pro Pro
1 5 10 15

TCC AAG ACC TAC CGA GGA GCT TTC CAG AAT CTG TTC CAG AGC GTG CGC 455
Ser Lys Thr Tyr Arg Gly Ala Phe Gln Asn Leu Phe Gln Ser Val Arg
20 25 30

GAA GTG ATC CAG AAC CCG GGC CCC AGG CAC CCA GAG GCC GCG AGC GCA 503
Glu Val Ile Gln Asn Pro Gly Pro Arg His Pro Glu Ala Ala Ser Ala
35 40 45

GCA CCT CCC GGC GCC AGT TTG CTG CTG CTG CAG CAG CAG CAG CAG CAG 551
Ala Pro Pro Gly Ala Ser Leu Leu Leu Leu Gln Gln Gln Gln Gln Gln
50 55 60

CAG CAG CAG CAG CAG CAG CAG CAG CAG CAG CAG CAG CAG CAG CAA GAG 599
Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Glu
65 70 75

ACT AGC CCC AGG CAG CAG CAG CAG CAG CAG GGT GAG GAT GGT TCT CCC 647
Thr Ser Pro Arg Gln Gln Gln Gln Gln Gln Gly Glu Asp Gly Ser Pro
80 85 90 95

CAA GCC CAT CGT AGA GGC CCC ACA GGC TAC CTG GTC CTG GAT GAG GAA 695
Gln Ala His Arg Arg Gly Pro Thr Gly Tyr Leu Val Leu Asp Glu Glu
100 105 110

CAG CAA CCT TCA CAG CCG CAG TCG GCC CTG GAG TGC CAC CCC GAG AGA 743
Gln Gln Pro Ser Gln Pro Gln Ser Ala Leu Glu Cys His Pro Glu Arg
115 120 125

GGT TGC GTC CCA GAG CCT GGA GCC GCC GTG GCC GCC AGC AAG GGG CTG 791
Gly Cys Val Pro Glu Pro Gly Ala Ala Val Ala Ala Ser Lys Gly Leu
130 135 140

CCG CAG CAG CTG CCA GCA CCT CCG GAC GAG GAT GAC TCA GCT GCC CCA 839
Pro Gln Gln Leu Pro Ala Pro Pro Asp Glu Asp Asp Ser Ala Ala Pro
145 150 155

TCC ACG TTG TCC CTG CTG GGC CCC ACT TTC CCC GGC TTA AGC AGC TGC 887
Ser Thr Leu Ser Leu Leu Gly Pro Thr Phe Pro Gly Leu Ser Ser Cys
160 165 170 175

TCC GCT GAC CTT AAA GAC ATC CTG AGC GAG GCC AGC ACC ATG CAA CTC 935
Ser Ala Asp Leu Lys Asp Ile Leu Ser Glu Ala Ser Thr Met Gln Leu
180 185 190

CTT CAG CAA CAG CAG CAG GAA GCA GTA TCC GAA GGC AGC AGC AGC GGG 983
Leu Gln Gln Gln Gln Gln Glu Ala Val Ser Glu Gly Ser Ser Ser Gly
195 200 205

AGA GCG AGG GAG GCC TCG GGG GCT CCC ACT TCC TCC AAG GAC AAT TAC 1031
Arg Ala Arg Glu Ala Ser Gly Ala Pro Thr Ser Ser Lys Asp Asn Tyr
210 215 220

TTA GGG GGC ACT TCG ACC ATT TCT GAC AAC GCC AAG GAG TTG TGT AAG 1079
Leu Gly Gly Thr Ser Thr Ile Ser Asp Asn Ala Lys Glu Leu Cys Lys
225 230 235

GCA GTG TCG GTG TCC ATG GGC CTG GGT GTG GAG GCG TTG GAG CAT CTG 1127
Ala Val Ser Val Ser Met Gly Leu Gly Val Glu Ala Leu Glu His Leu
240 245 250 255

AGT CCA GGG GAA CAG CTT CGG GGG GAT TGC ATG TAC GCC CCA CTT TTG 1175
Ser Pro Gly Glu Gln Leu Arg Gly Asp Cys Met Tyr Ala Pro Leu Leu
260 265 270

GGA GTT CCA CCC GCT GTG CGT CCC ACT CCT TGT GCC CCA TTG GCC GAA 1223
Gly Val Pro Pro Ala Val Arg Pro Thr Pro Cys Ala Pro Leu Ala Glu
275 280 285

TGC AAA GGT TCT CTG CTA GAC GAC AGC GCA GGC AAG AGC ACT GAA GAT 1271
Cys Lys Gly Ser Leu Leu Asp Asp Ser Ala Gly Lys Ser Thr Glu Asp
290 295 300

ACT GCT GAG TAT TCC CCT TTC AAG GGA GGT TAC ACC AAA GGG CTA GAA 1319
Thr Ala Glu Tyr Ser Pro Phe Lys Gly Gly Tyr Thr Lys Gly Leu Glu
305 310 315

GGC GAG AGC CTA GGC TGC TCT GGC AGC GCT GCA GCA GGG AGC TCC GGG 1367
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320 325 330 335

ACA CTT GAA CTG CCG TCT ACC CTG TCT CTC TAC AAG TCC GGA GCA CTG 1415
Thr Leu Glu Leu Pro Ser Thr Leu Ser Leu Tyr Lys Ser Gly Ala Leu
340 345 350

GAC GAG GCA GCT GCG TAC CAG AGT CGC GAC TAC TAC AAC TTT CCA CTG 1463
Asp Glu Ala Ala Ala Tyr Gln Ser Arg Asp Tyr Tyr Asn Phe Pro Leu
355 360 365

GCT CTG GCC GGA CCG CCG CCC CCT CCG CCG CCT CCC CAT CCC CAC GCT 1511
Ala Leu Ala Gly Pro Pro Pro Pro Pro Pro Pro Pro His Pro His Ala
370 375 380

CGC ATC AAG CTG GAG AAC CCG CTG GAC TAC GGC AGC GCC TGG GCG GCT 1559
Arg Ile Lys Leu Glu Asn Pro Leu Asp Tyr Gly Ser Ala Trp Ala Ala
385 390 395

GCG GCG GCG CAG TGC CGC TAT GGG GAC CTG GCG AGC CTG CAT GGC GCG 1607
Ala Ala Ala Gln Cys Arg Tyr Gly Asp Leu Ala Ser Leu His Gly Ala
400 405 410 415

GGT GCA GCG GGA CCC GGT TCT GGG TCA CCC TCA GCC GCC GCT TCC TCA 1655
Gly Ala Ala Gly Pro Gly Ser Gly Ser Pro Ser Ala Ala Ala Ser Ser
420 425 430

TCC TGG CAC ACT CTC TTC ACA GCC GAA GAA GGC CAG TTG TAT GGA CCG 1703
Ser Trp His Thr Leu Phe Thr Ala Glu Glu Gly Gln Leu Tyr Gly Pro
435 440 445

TGT GGT GGT GGT GGG GGT GGT GGC GGC GGC GGC GGC GGC GGC GGC GGC 1751
Cys Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly
450 455 460

GGC GGC GGC GGC GGC GGC GGC GGC GGC GAG GCG GGA GCT GTA GCC CCC 1799
Gly Gly Gly Gly Gly Gly Gly Gly Gly Glu Ala Gly Ala Val Ala Pro
465 470 475

TAC GGC TAC ACT CGG CCC CCT CAG GGG CTG GCG GGC CAG GAA AGC GAC 1847
Tyr Gly Tyr Thr Arg Pro Pro Gln Gly Leu Ala Gly Gln Glu Ser Asp
480 485 490 495

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Phe Thr Ala Pro Asp Val Trp Tyr Pro Gly Gly Met Val Ser Arg Val
500 505 510

CCC TAT CCC AGT CCC ACT TGT GTC AAA AGC GAA ATG GGC CCC TGG ATG 1943
Pro Tyr Pro Ser Pro Thr Cys Val Lys Ser Glu Met Gly Pro Trp Met
515 520 525

GAT AGC TAC TCC GGA CCT TAC GGG GAC ATG CGT TTG GAG ACT GCC AGG 1991
Asp Ser Tyr Ser Gly Pro Tyr Gly Asp Met Arg Leu Glu Thr Ala Arg
530 535 540

GAC CAT GTT TTG CCC ATT GAC TAT TAC TTT CCA CCC CAG AAG ACC TGC 2039
Asp His Val Leu Pro Ile Asp Tyr Tyr Phe Pro Pro Gln Lys Thr Cys
545 550 555

CTG ATC TGT GGA GAT GAA GCT TCT GGG TGT CAC TAT GGA GCT CTC ACA 2087
Leu Ile Cys Gly Asp Glu Ala Ser Gly Cys His Tyr Gly Ala Leu Thr
560 565 570 575

TGT GGA AGC TGC AAG GTC TTC TTC AAA AGA GCC GCT GAA GGG AAA CAG 2135
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580 585 590

AAG TAC CTG TGC GCC AGC AGA AAT GAT TGC ACT ATT GAT AAA TTC CGA 2183
Lys Tyr Leu Cys Ala Ser Arg Asn Asp Cys Thr Ile Asp Lys Phe Arg
595 600 605

AGG AAA AAT TGT CCA TCT TGT CGT CTT CGG AAA TGT TAT GAA GCA GGG 2231
Arg Lys Asn Cys Pro Ser Cys Arg Leu Arg Lys Cys Tyr Glu Ala Gly
610 615 620

ATG ACT CTG GGA GCC CGG AAG CTG AAG AAA CTT GGT AAT CTG AAA CTA 2279
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CAG GAG GAA GGA GAG GCT TCC AGC ACC ACC AGC CCC ACT GAG GAG ACA 2327
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640 645 650 655

ACC CAG AAG CTG ACA GTG TCA CAC ATT GAA GGC TAT GAA TGT CAG CCC 2375
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660 665 670

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785 790 795

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Thr Pro Gln Glu Phe Leu Cys Met Lys Ala Leu Leu Leu Phe Ser Ile
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835 840 845

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900 905 910

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Lys Pro Ile Tyr Phe His Thr Gln
915 920

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ATTTGCTGGG CTTTTTTTTT CTCTTTCTCT CCTTTCTTTT TCTTCTTCCC TCCCTATCTA 3329

ACCCTCCCAT GGCACCTTCA GACTTTGCTT CCCATTGTGG CTCCTATCTG TGTTTTGAAT 3389

GGTGTTGTAT GCCTTTAAAT CTGTGATGAT CCTCATATGG CCCAGTGTCA AGTTGTGCTT 3449

GTTTACAGCA CTACTCTGTG CCAGCCACAC AAACGTTTAC TTATCTTATG CCACGGGAAG 3509

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(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1082 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: HOMO SAPIENS

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION: 602..770

(D) OTHER INFORMATION: /note= "SEGMENT 1 OF 3."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

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GCCCTGGAAA CCCCTCCCAG GCCTGGGACC ATCCTTCCTT AACCACCAGC CACCTCACAG 420

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ACTACAGGTT TGTTCAATTT CTTACAGTCT TGAAAGCGCC ACAAGCAGCA GCTGCTGAGC 600

CATGGCTGAA GGGGAAATCA CCACCTTCAC AGCCCTGACC GAGAAGTTTA ATCTGCCTCC 660

AGGGAATTAC AAGAAGCCCA AACTCCTCTA CTGTAGCAAC GGGGGCCACT TCCTGAGGAT 720

CCTTCCGGAT GGCACAGTGG ATGGGACAAG GGACAGGAGC GACCAGCACA GTAAGCCCAT 780

CTCTATGGCA CCCCCCTTCC CTTTCTGACA TCTTCTGTAG TCAAGGTGGG AGGAAGGTGC 840

ACATTTAAGT ACAGGTACTT GCTTCTCCAA GGTTCTATTC AGGCATGACA CATTCAGAGG 900

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CT 1082

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 427 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: HOMO SAPIENS

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION: 186..289
(D) OTHER INFORMATION: /note= "SEGMENT 2 OF 3. UNKNOWN NUMBER OF BP AFTER SEGMENT 1."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

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CTGCCGGGTC CTATCGGCAA AAGCGTAGTG TTTATTTACT TTTGCTCGTG TTATTTTTAT 180

TCCAGTTCAG CTGCAGCTCA GTGCGGAAAG CGTGGGGGAG GTGTATATAA AGAGTACCGA 240

GACTGGCCAG TACTTGGCCA TGGACACCGA CGGGCTTTTA TACGGCTCAG TAAGTATGAA 300

GCTGACATGC TTCCAGACGT TGGCCAAGGT TTGAGGTTTC CAGAAATCTT GTTACATGGA 360

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CACCCTC 427

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 664 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: HOMO SAPIENS

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION: 304..498
(D) OTHER INFORMATION: /note= "SEGMENT 3 OF 3. UNKNOWN NUMBER OF BP AFTER SEGMENT 2."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

TGAGGACTCT TAGAAGTGCT CTTATCAGTA GCATCTTAAT TACTTTACAA TGGATTTTAA 60

ATGGAAAGGA AGTTTACAAT AATAGCAAAT GCATATTGAC AGCTCTTTAG TGCCCGGTGC 120

TGTTCTAAGT CCTTATGACT ACCCTGTGAA ATAAGTTCCA CCATGACCCC AATTTTCCTG 180

AAAAGGAGAC TGAGGCATGG AGAGCTTTAG TATTTTGCCC AATGTCACAC AGCTAGTAAA 240

TGGGGACCCC CATGTGAAAC TACTCACTGA TTGTCCTACT CTCTTGTGGT TTTATCTTTT 300

TAGCAGACAC CAAATGAGGA ATGTTTGTTC CTGGAAAGGC TGGAGGAGAA CCATTACAAC 360

ACCTATATAT CCAAGAAGCA TGCAGAGAAG AATTGGTTTG TTGGCCTCAA GAAGAATGGG 420

AGCTGCAAAC GCGGTCCTCG GACTCACTAT GGCCAGAAAG CAATCTTGTT TCTCCCCCTG 480

CCAGTCTCTT CTGATTAAAG AGATCTGTTC TGGGTGTTGA CCACTCCAGA GAAGTTTCGA 540

GGGGTCCTCA CCTGGTTGAC CCAAAAATGT TCCCTTGACC ATTGGCTGCG CTAACCCCCA 600

GCCCACAGAG CCTGAATTTG TAAGCAACTT GCTTCTAAAT GCCCAGTTCA CTTCTTTGCA 660

GAGC 664

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: YES

(vi) ORIGINAL SOURCE:
(A) ORGANISM: SYNTHETIC OLIGONUCLEOTIDE

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 1..27
(D) OTHER INFORMATION: /note= "ANTISENSE TO POSITIONS 927-953 OF SEQ ID NO.: 1."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

CTGCTGCTGT TGCTGAAGGA GTTGCAT 27

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: YES

(vi) ORIGINAL SOURCE:
(A) ORGANISM: SYNTHETIC OLIGONUCLEOTIDE

(ix) FEATURE:
(A) NAME/KEY: misc_feature

(B) LOCATION: 1..21

(D) OTHER INFORMATION: /note= "ANTISENSE TO POSITIONS 916-936 OF SEQ ID NO.: 1."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

GGAGTTGCAT GGTGCTGGCC TCAGCACCA 29

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 29 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: YES

(vi) ORIGINAL SOURCE:

(A) ORGANISM: SYNTHETIC OLIGONUCLEOTIDE

(ix) FEATURE:

(A) NAME/KEY: misc_feature

(B) LOCATION: 1..21

(D) OTHER INFORMATION: /note= "ANTISENSE TO POSITIONS 927-947 OF SEQ ID NO.: 1."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

CTGTTGCTGA AGGAGTTGCA TAACTCCTT 29

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 25 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: YES

(vi) ORIGINAL SOURCE:

(A) ORGANISM: SYNTHETIC OLIGONUCLEOTIDE

(ix) FEATURE:

(A) NAME/KEY: misc_feature

(B) LOCATION: 1..25

(D) OTHER INFORMATION: /note= "ANTISENSE TO POSITIONS 611-635 OF SEQ ID NO.: 2."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

GGGCTGTGAA GGTGGTGATT TCCCC 25

# INTERNATIONAL SEARCH REPORT

International application No
PCT/US 96/15081

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/11 C07H21/04 A61K31/70 //A61K48/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N C07H A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 94 05268 A (BAYLOR COLLEGE MEDICINE) 17 March 1994<br>see page 8, line 14 - page 10, line 20<br>see example 1<br>see claims 1,2,17-21,32-35<br>--- | 1,7,13, 15,21, 28,29 |
| X | WO 89 09791 A (UNIV NORTH CAROLINA) 19 October 1989<br>see page 2, line 12 - line 32<br>see page 24<br>--- | 1,28,29 |
| X | WO 95 11301 A (UNIV MICHIGAN) 27 April 1995<br>see claims<br>---<br>-/-- | 28,29 |

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 14 February 1997 | 26.02.97 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax (+31-70) 340-3016 | Andres, S |

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | CANCER RESEARCH, (1994 MAY 1) 54 (9) 2372-7., XP002025258<br>ACHBAROU, A. ET AL.: "Urokinase overproduction results in increased skeletal metastasis by prostate cancer cells in vivo."<br>see the whole document | 28,29 |
| A | CANCER SURVEYS, vol. 11, 1991, pages 239-254, XP000616360<br>SHERIDAN, V. & TEW, K.: "Mechanism based chemotherapy for prostate cancer"<br>cited in the application<br>see the whole document | 12,26 |
| O,A | ANTISENSE RES.DEV. 5 ( FALL 1995); PAGE 239; ABSTRACT III12, XP002025259<br>HEAD, M. ET AL.: "Penetration and stability of antisense oligonucleotides injected into the early embryonic chick eye"<br>see abstract<br>& INT.CONF.:'THERAPEUTIC OLIGONUCLEOTIDES FROM CELL TO MAN'; 4 TO 7 APRIL 1995; SEILLAC; FRANCE, | 1,4-9 |
| P,X | US 5 556 956 A (ROY ARUN K ET AL) 17 September 1996<br>see the whole document | 1,7-10, 13,15, 21-24, 27-29 |
| P,X | CELL GROWTH AND DIFFERENTIATION, (1996 MAY) 7 (5) 573-86., XP000616505<br>SHAIN, S. ET AL.: "Endogenous fibroblast growth factor - 1 or fibroblast growth factor -2 modulate prostate cancer cell proliferation."<br>see the whole document | 1,4-9, 28,29 |
| P,X | JOURNAL OF BIOLOGICAL CHEMISTRY, (1996 MAY 31) 271 (22) 13228-33., XP002025260<br>BOFFA, L. ET AL.: "Invasion of the CAG triplet repeats by a complementary peptide nucleic acid inhibits transcription of the androgen receptor and TATA-binding protein genes and correlates with refolding of an active nucleosome containing a unique AR gene sequence."<br>see the whole document | 1-3,7,8, 10,28,29 |
| P,X | WO 96 03875 A (UNIV EMORY) 15 February 1996 | 28,29 |
| P,A | see page 11, line 12 - page 13, line 21 | 12,26 |

-/--

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| O,P, X | PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL MEETING 37 (0), March 1996, page 344 XP002025261 STEINER, M. ET AL.: "Gene therapy of advanced prostate cancer by in vivo transduction with prostate-targeted antisense c- myc RNA retroviruses." see abstract #2349 & 87TH ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, WASHINGTON, D.C., USA, APRIL 20-24, 1996., ----- | 28,29 |

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

Interna al application No.
PCT/US 96/ 15081

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Please see Further Information sheet enclosed.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant s protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 96/ 15081

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

Remark : Although claims 1-14, 28-29 (as far as in vivo methods are concerned) are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 96/15081

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO-A-9405268 | 17-03-94 | AU-A- 4846793 | 29-03-94 |
| WO-A-8909791 | 19-10-89 | EP-A- 0365657 | 02-05-90 |
| WO-A-9511301 | 27-04-95 | AU-A- 7983294 | 08-05-95 |
| US-A-5556956 | 17-09-96 | NONE | |
| WO-A-9603875 | 15-02-96 | AU-A- 3071995 | 04-03-96 |